CENTER FOR DRUG EVALUATION AND RESEARCH

Shedding Some Light on FDA Inspections of Clinical Drug Trials

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Office of Scientific Investigations
Office of Compliance
CDER/FDA

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Objectives

- Describe FDA's bioresearch monitoring (BIMO) program
- Identify the federal regulations covering clinical research and clinical investigator obligations
- Discuss what to expect during and after an FDA inspection
- Discuss specific problems seen during recent FDA inspections at clinical sites
- Discuss various methods that can be used to ensure compliance with federal regulations

FDA's Bioresearch Monitoring Program

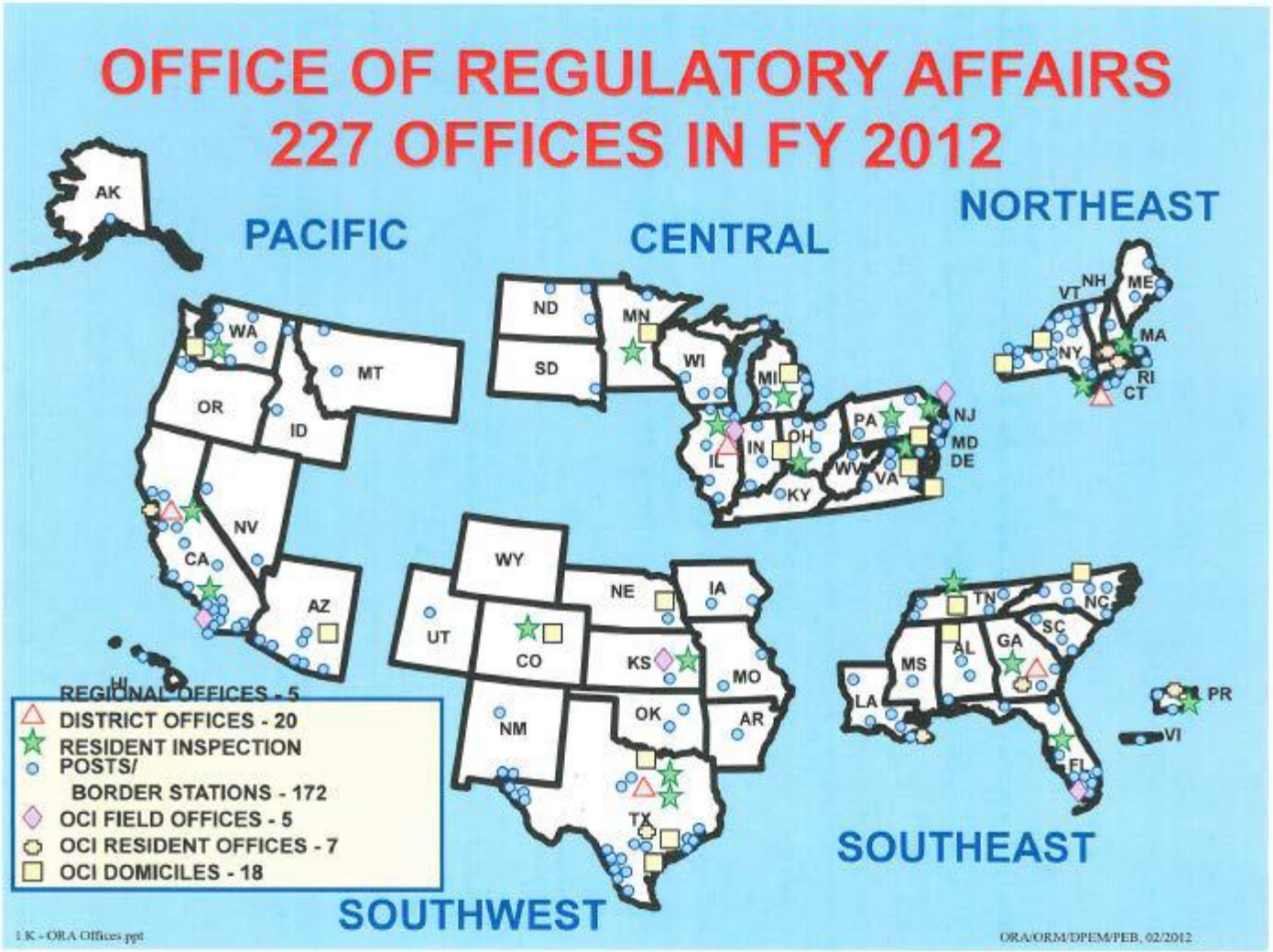
- A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.
- The Program was **established in 1977** to verify the data submitted in support of marketing applications and to provide oversight of the conduct of studies with regulated products.
  - First FDA inspection of a clinical investigator was in 1961 in Maryland. The CI was convicted after it was determined that most of the results were produced at the kitchen table (> 25 sponsors)
  - In early 1960's Mer-29 (cholesterol lowering agent) data was falsified and toxicity data not submitted (liver damage, cataracts)

BIMO Program Responsibilities

- **Evaluates adherence to applicable regulations with respect to:**
  - Good Clinical Practice (GCP)
    - Clinical Investigators
    - Sponsors, Monitors, Contract Research Organizations
    - Institutional Review Boards
  - Good Laboratory Practice (GLP)
  - *In vivo* Bioequivalence (BE)

"The Field"

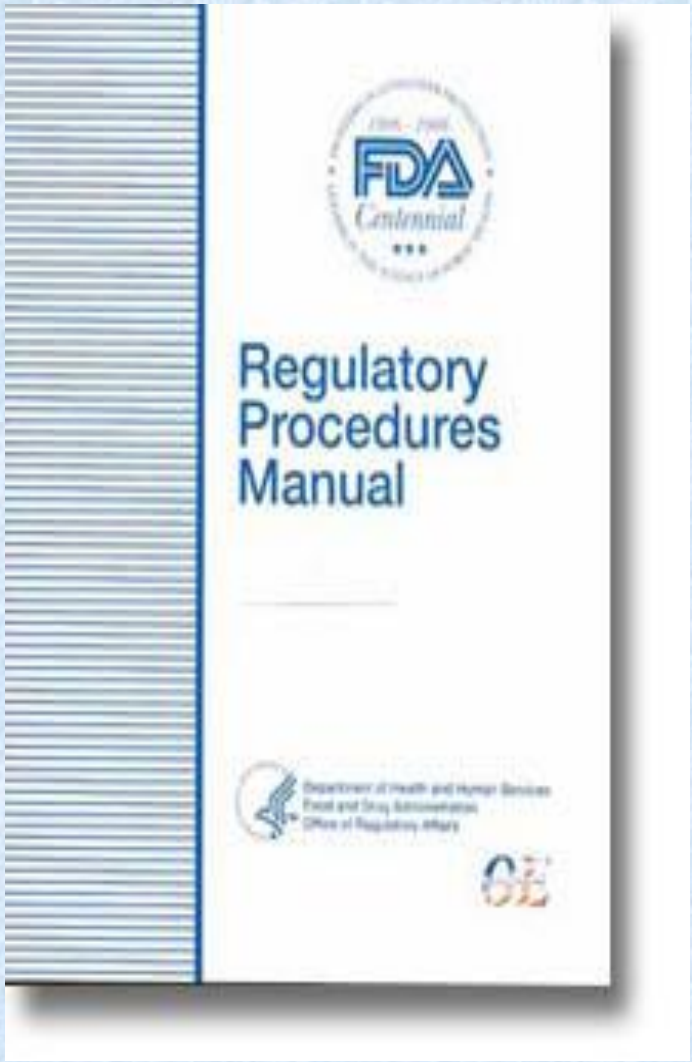
- Refers to FDA offices within the Office of Regulatory Affairs (ORA)
- Located in 5 major regions of US:
  - 5 "Regional Offices"
  - 20 "District Offices"
    - 50 - 100 staff per office
    - 1 "District Office" is imports only
  - Over 200 locations across country
    - Includes approximately 140 "Resident Posts"


OFFICE OF REGULATORY AFFAIRS
227 OFFICES IN FY 2012
PACIFIC
CENTRAL
NORTHEAST
SOUTHWEST
SOUTHEAST
AK
HI
WA
OR
CA
ID
NV
MT
AZ
ND
SD
MN
WI
MI
IL
IN
OH
KY
WV
VA
PA
NJ
MD
DE
VT
NH
ME
NY
MA
RI
CT
WY
NE
IA
UT
CO
KS
MO
NM
OK
AR
TX
TN
NC
SC
GA
AL
MS
LA
FL
PR
VI
REGIONAL OFFICES - 5
DISTRICT OFFICES - 20
RESIDENT INSPECTION POSTS/
BORDER STATIONS - 172
OCI FIELD OFFICES - 5
OCI RESIDENT OFFICES - 7
OCI DOMICILES - 18
1 K - ORA Offices.ppt
ORA/ORM/DPEM/PEB, 02/2012

Compliance Program Guidance Manuals (CPGM)

- **Provide guidance and instructions to FDA staff conducting inspections**
  - 7348.001 In Vivo Bioequivalence
  - 7348.808 Good Laboratory Practice (Nonclinical Laboratories)
  - 7348.809 Institutional Review Board
    - 7348.809A Radioactive Drug Research Committee
  - 7348.810 Sponsors, Contract Research Organizations, and Monitors
  - 7348.811 Clinical Investigators

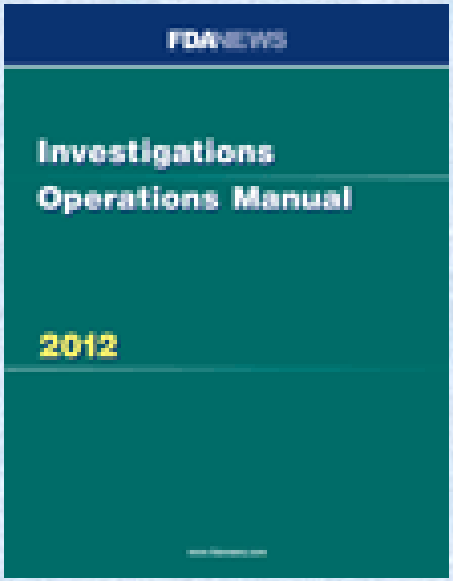
http://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograManual/ucm255614.htm



- Chapter 1 - Regulatory Organization
- Chapter 2 - FDA Authority
- Chapter 3 - Commissioning and Work Sharing
- Chapter 4 - Advisory Actions
- Chapter 5 - Administrative Actions
- Chapter 6 - Judicial Actions
- Chapter 7 - Recall Procedures
- Chapter 8 - Emergency Procedures
- Chapter 9 - Import Operations and Actions
- Chapter 10 - Other Procedures
- Chapter 11 - Glossary
- Appendix
- Chapter Summary

http://www.fda.gov/ICECI/compliancemanuals/regulatoryproceduresmanual/default.htm

Investigations Operations Manual



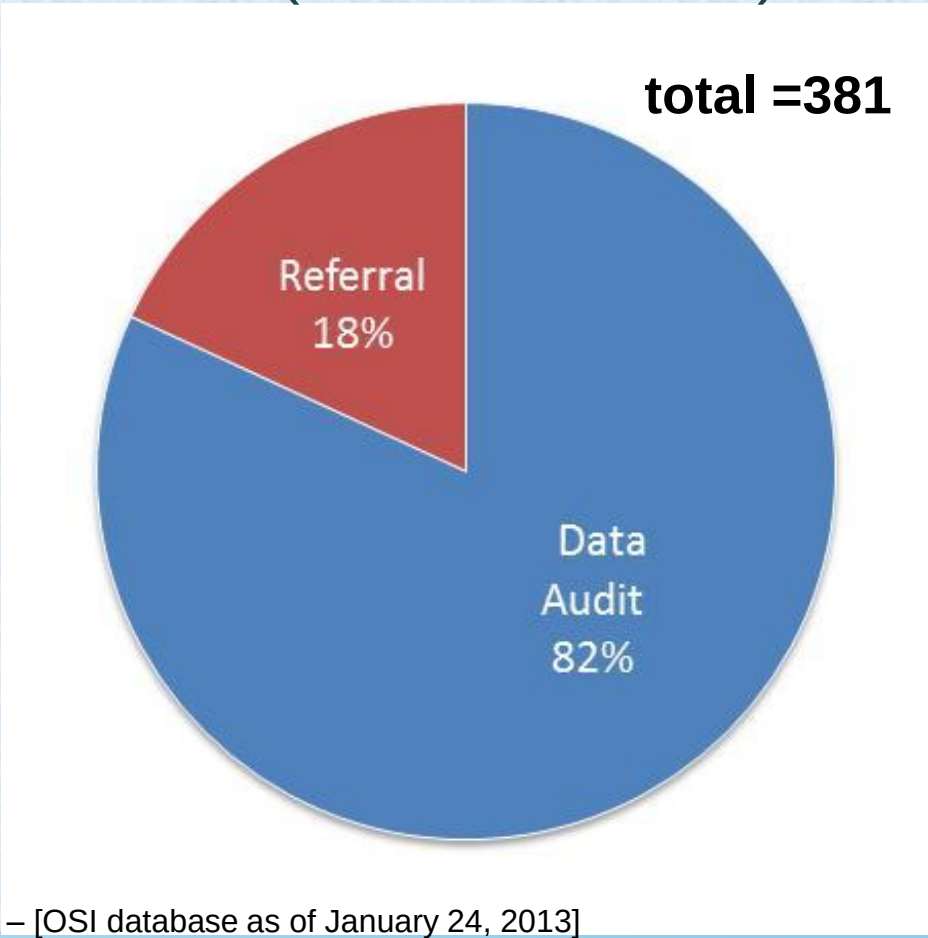
- Chapter 1 - Administration
- Chapter 2 - Regulatory
- Chapter 3 - Federal and State Cooperation
- Chapter 4 - Sampling
- Chapter 5 - Establishment Inspections
- Chapter 6 - Imports
- Chapter 7 - Recall
- Chapter 8 - Investigations
- IOM Appendix
- IOM Index
- IOM ORA Directory
- IOM Sample Schedules

http://www.fda.gov/ICECI/Inspections/IOM/default.htm

PDUFA (Prescription Drug User Fee Act)-Related Inspections vs For-Cause

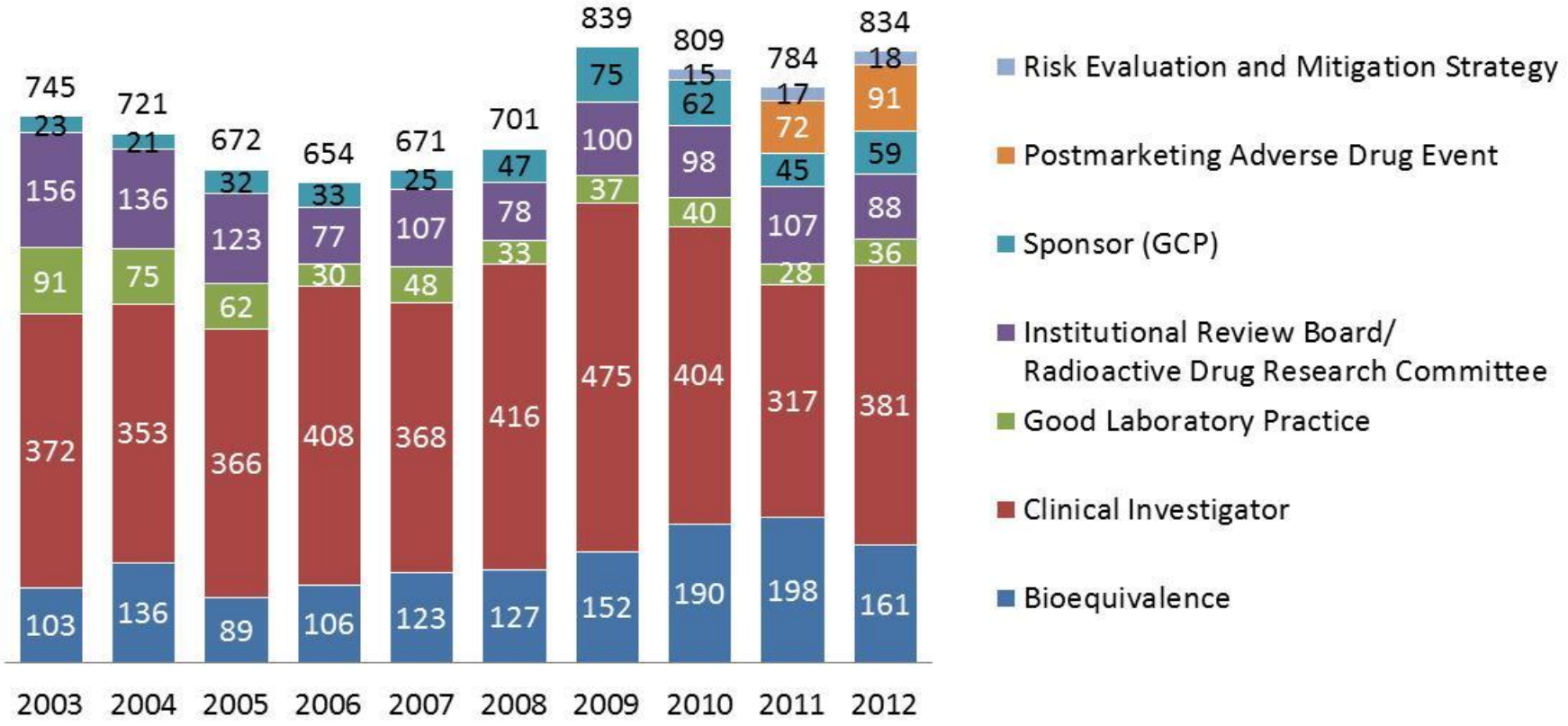
- **PDUFA-Related Inspections (NDA/BLA)**
  - Done in support of marketing applications
    - Drug is typically a new molecular entity (NME)
    - Pivotal studies contain non-IND/ foreign sites
  - Also may be referred to as "Routine" Inspections
  - Can be conducted at **any point** in the drug development process
- **For-Cause Inspections (Complaints)**
  - Based on complaints from any source
  - Allegations that raise concerns regarding data integrity or the rights, welfare, and safety of study subjects have been compromised

Clinical Investigator Inspections: Data Audit versus Referral * (CDER, FY 2012)



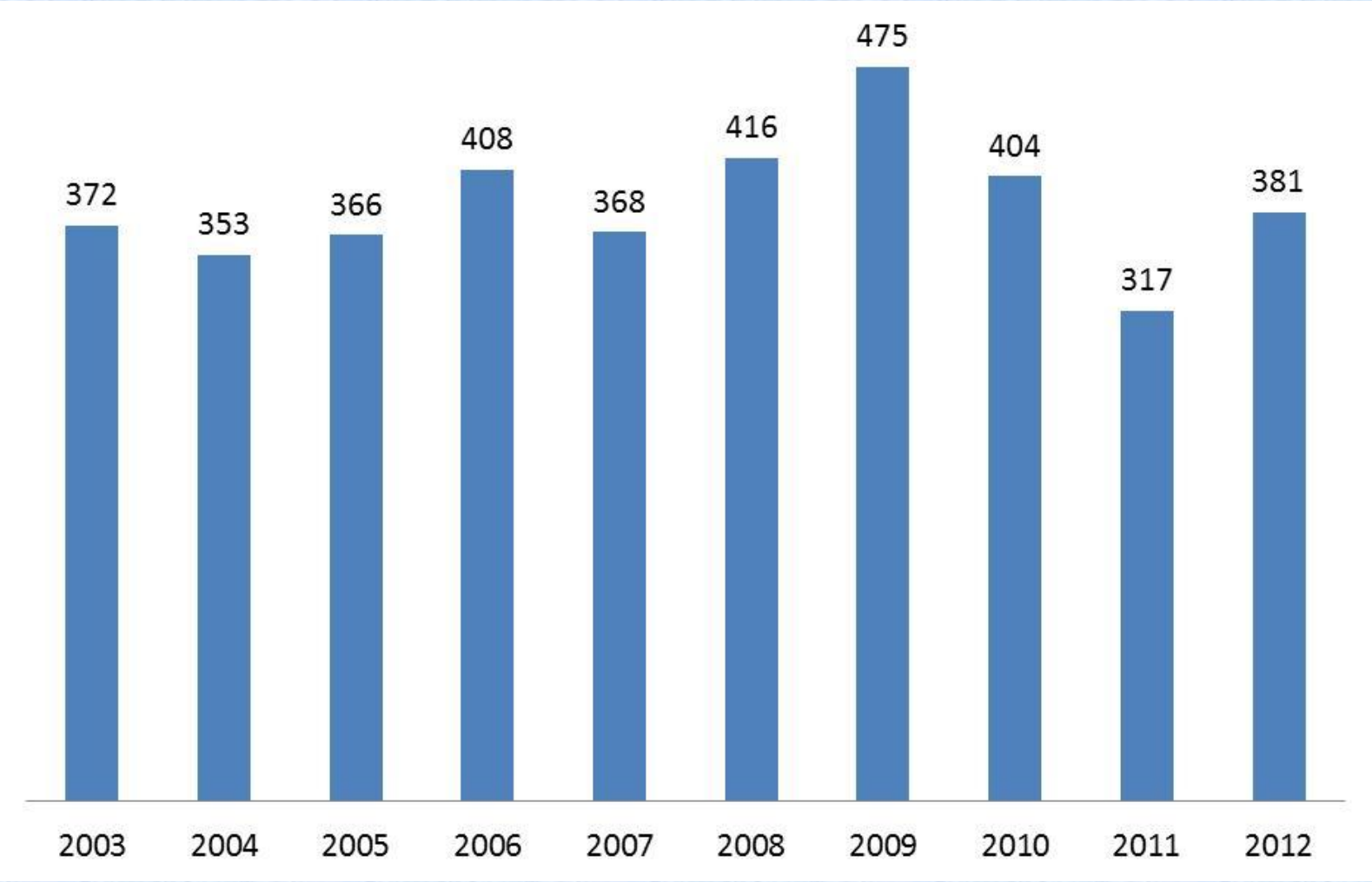
*Based on inspection start date – [OSI database as of January 24, 2013]
Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches

Inspections Overseen by OSI * (CDER, FY 2003 - FY 2012)



- *Based on inspection start date – [OSI database as of January 24, 2013]
- IRB includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH, Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- As of June 2011, Postmarketing Adverse Drug Event and Risk Evaluation and Mitigation Strategy inspection programs were incorporated into OSI

Clinical Investigator Inspections* (CDER, FY 2003 – FY 2012)



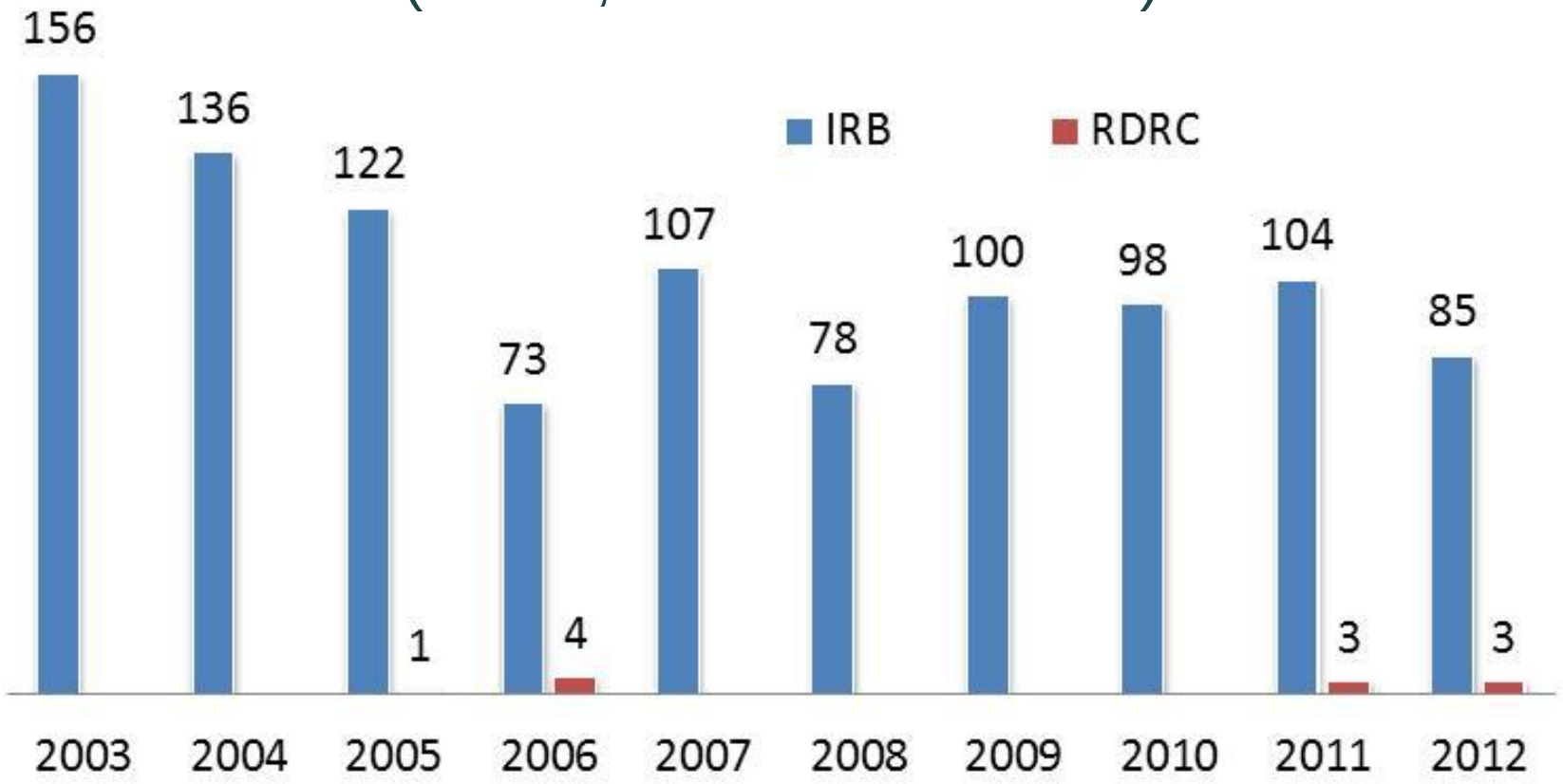
*Based on inspection start date – [OSI database as of January 24, 2013]

GCP-Related Sponsor/Contract Research Organization Inspections* (CDER, FY 2012)

*Based on inspection start date [OSI database as of January 24, 2013]

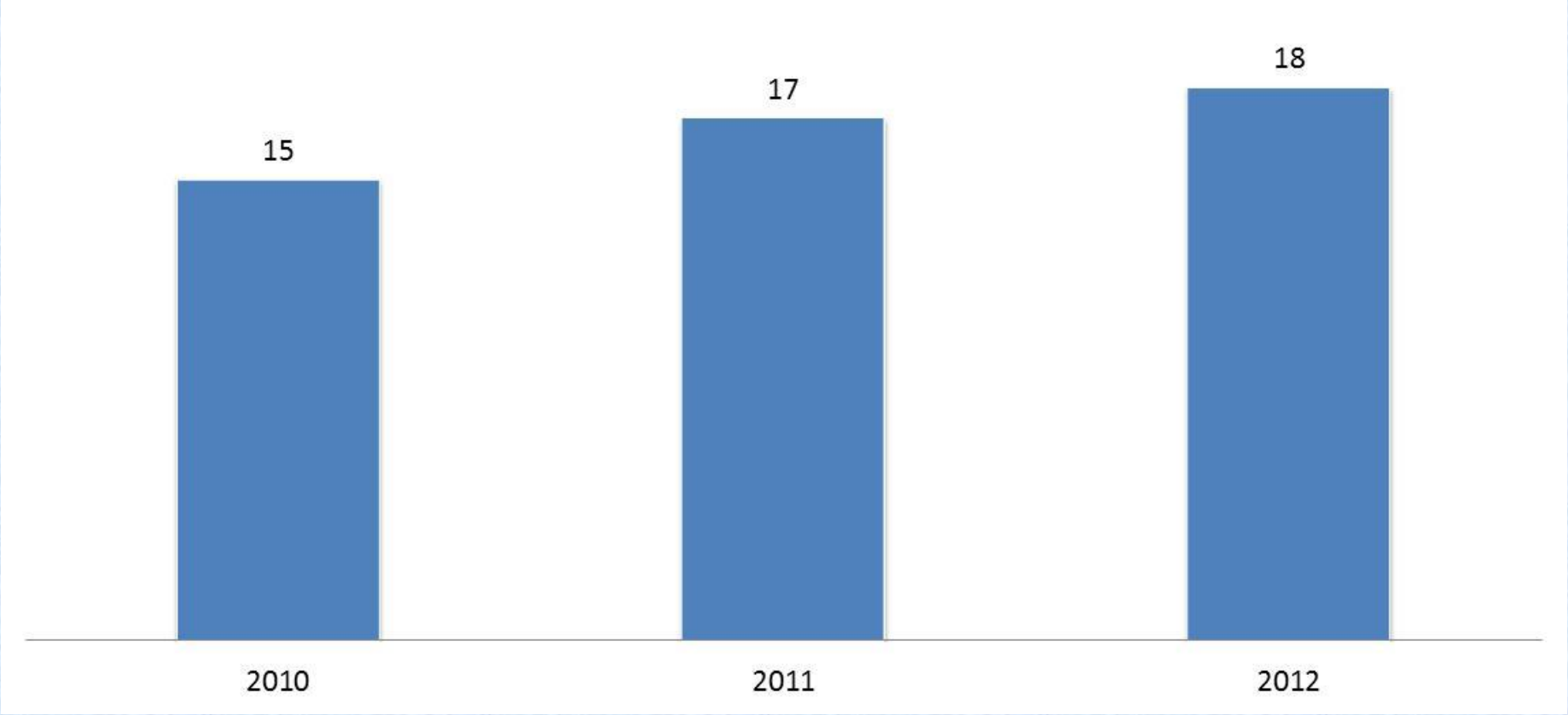
The Sponsor/CRO distribution shifted for FY09-11 in previous releases due to corrections in the OSI Database.

IRB/RDRC Inspections*
(CDER, FY 2003 - FY 2012)



*Based on inspection start date [OSI database as of January 24, 2013]
Includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH

Risk Evaluation and Mitigation Strategies Inspections* (CDER, FY 2010-2012)

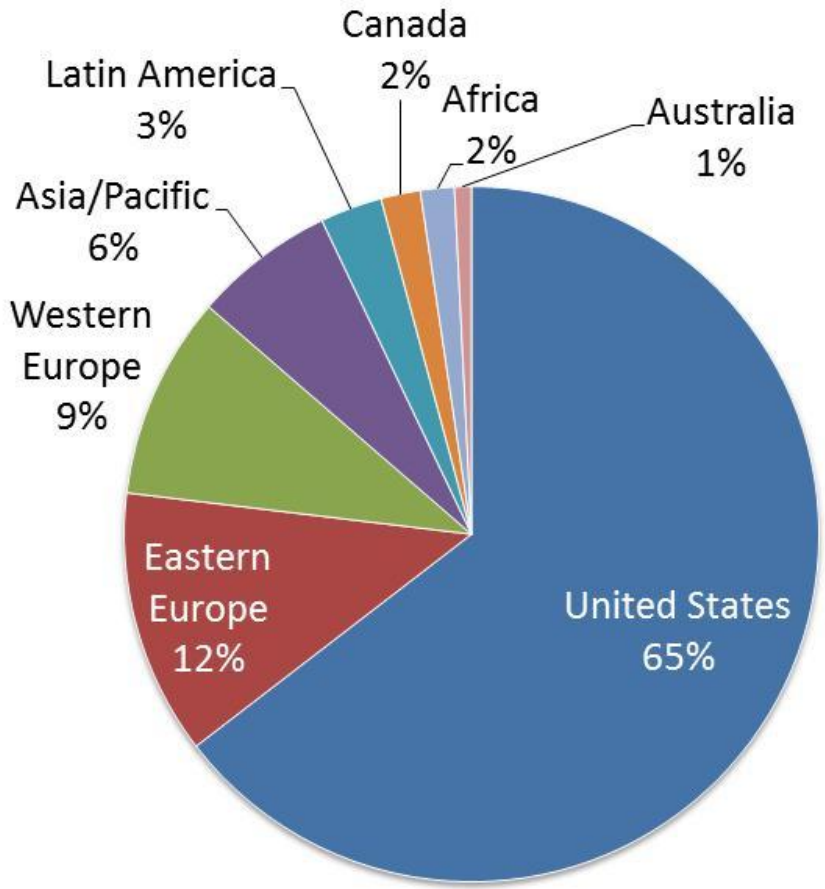


*Based on date inspection completed, REMS inspection program began in FY10

Clinical Investigator Inspections by Location*

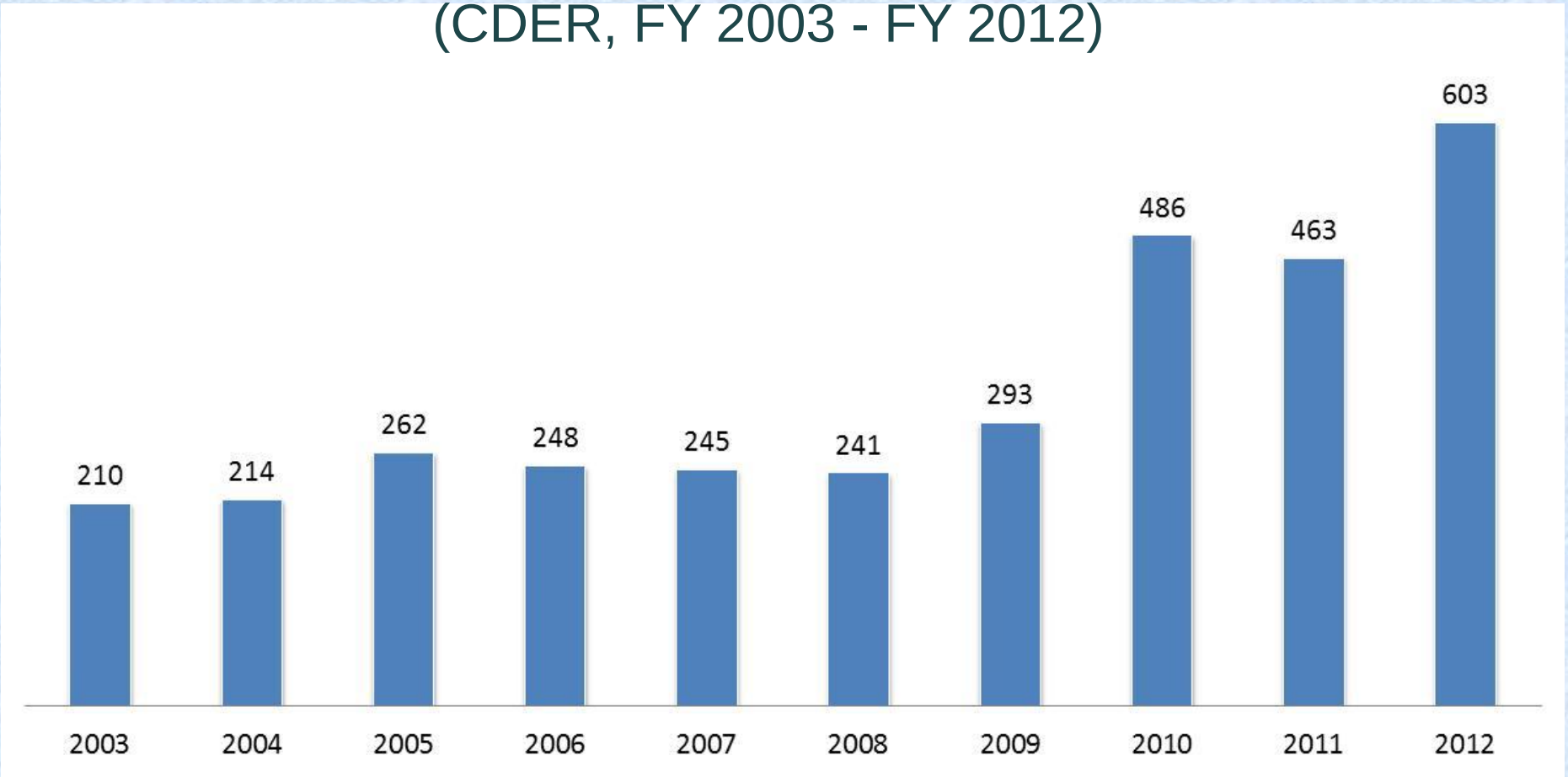
(CDER, FY 2012)

total =381



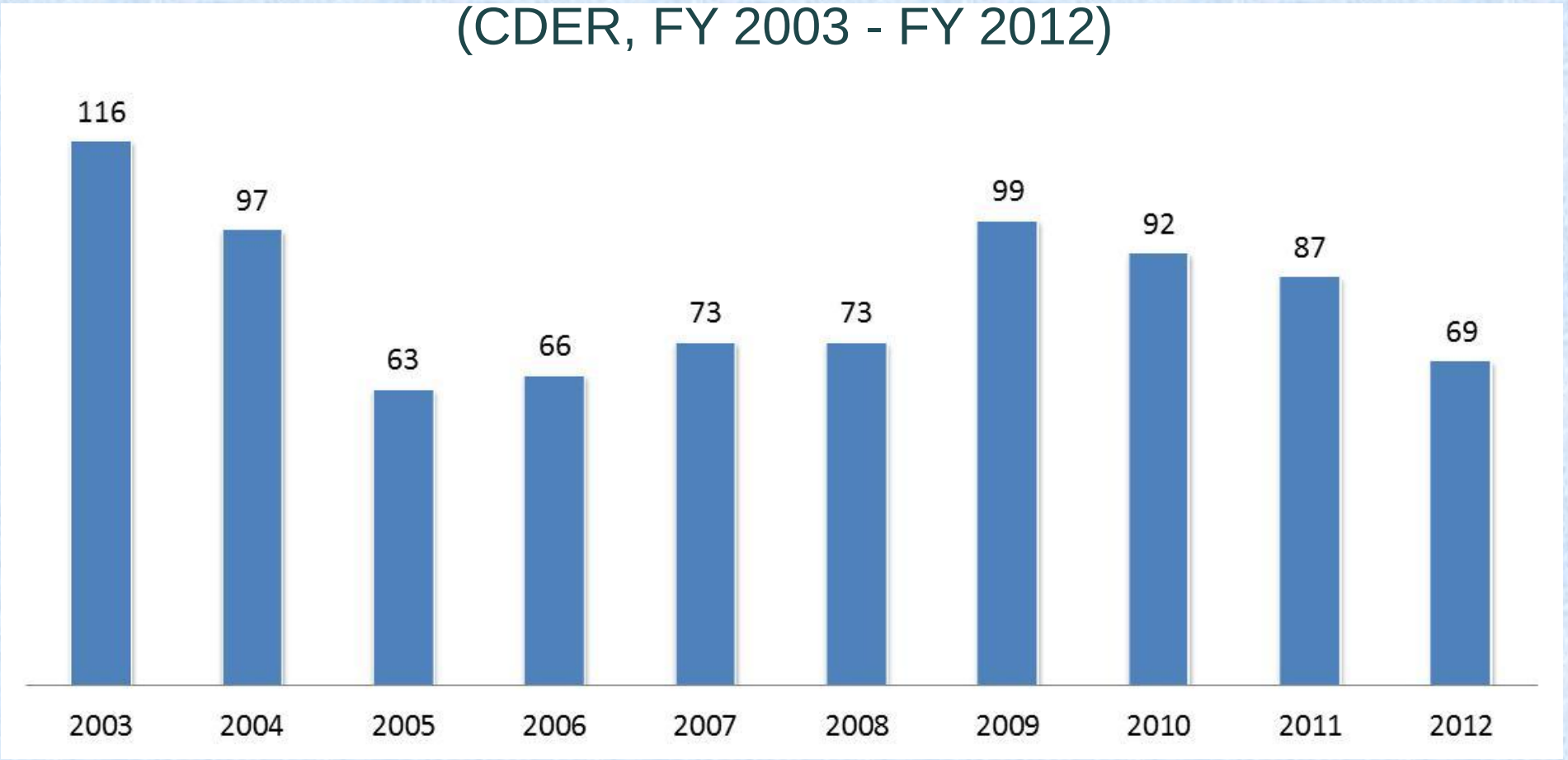
*Based on inspection start date – [OSI database as of January 24, 2013]

Referrals Received by OSI*
(CDER, FY 2003 - FY 2012)



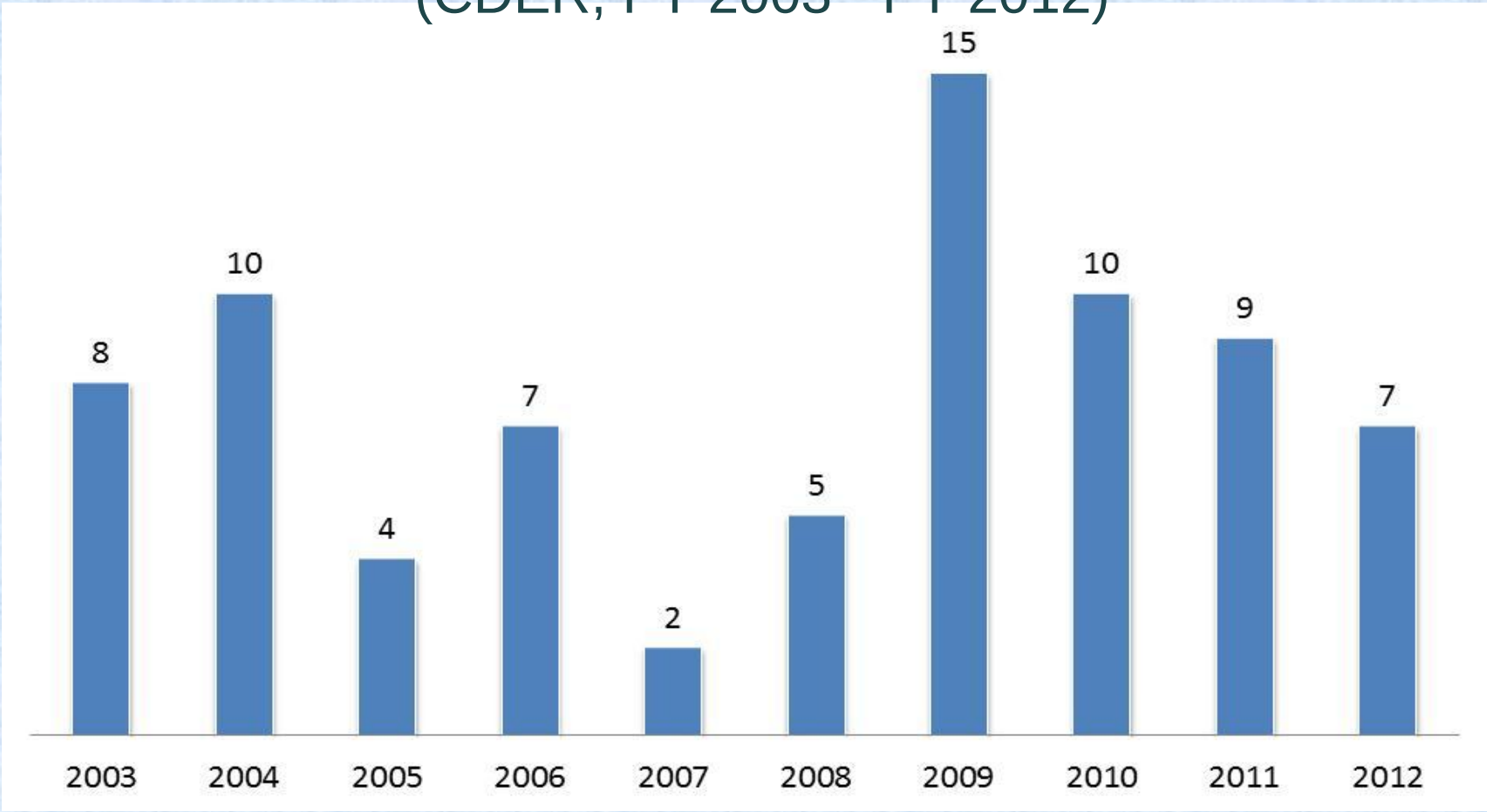
*Includes Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches – Evaluation may result in inspection
[OSI database as of January 15, 2013]

Referral-Related Clinical Investigator Inspections*
(CDER, FY 2003 - FY 2012)



*Based on inspection start date; Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches
[OSI database as of January 24, 2013]

Referral-Related Sponsor Inspections*
(CDER, FY 2003 - FY 2012)



*Based on inspection start date; Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches
[OSI database as of January 24, 2013]

Directed (For Cause) Inspection Criteria

- Suspicion of false or fraudulent data
- Evidence that a sponsor has rejected data from an investigator
- Evidence of delay in submitting adverse clinical findings
- Evidence of inadequately monitored clinical investigations
- Evidence of inadequate or inappropriate informed consent
- Evidence of delayed or inappropriate IRB approval
- Evidence that an investigator has a significant financial interest in the product

Regulatory Authority to Conduct Inspections/Audits

- Section 505(k)(2) of the Food, Drug, and Cosmetic Act mandates that FDA shall have **access** to and **copy** and **verify** the required clinical study records.

- **21 CFR 312.68**
  - "An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator…"

FDA/CDER GCP Regulations

- **21 Code of Federal Regulations (CFR)**
  - Part 11—ELECTRONIC RECORDS; ELECTROINIC SIGNATURES
  - Part 50--PROTECTION OF HUMAN SUBJECTS
  - Part 56--INSTITUTIONAL REVIEW BOARDS
  - Part 58--GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES
  - Part 312--INVESTIGATIONAL NEW DRUG APPLICATION
  - Part 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
  - Part 320--BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

These are legally enforceable requirements!

Inspectional Challenges

- More sites per trial with smaller enrollment numbers
- More foreign sites per trial
- Trial protocols are more complicated
- More studies per application/ more pediatric studies
- Subjects participating in more than one trial
- More outsourcing/delegation of responsibilities in trials, e.g., to contract research organizations, sub-investigators
- Regulations don't recognize many parties involved in trials, e.g., site management organizations (SMOs)
- Need to harmonize regulations domestically and internationally
- Constantly changing technology

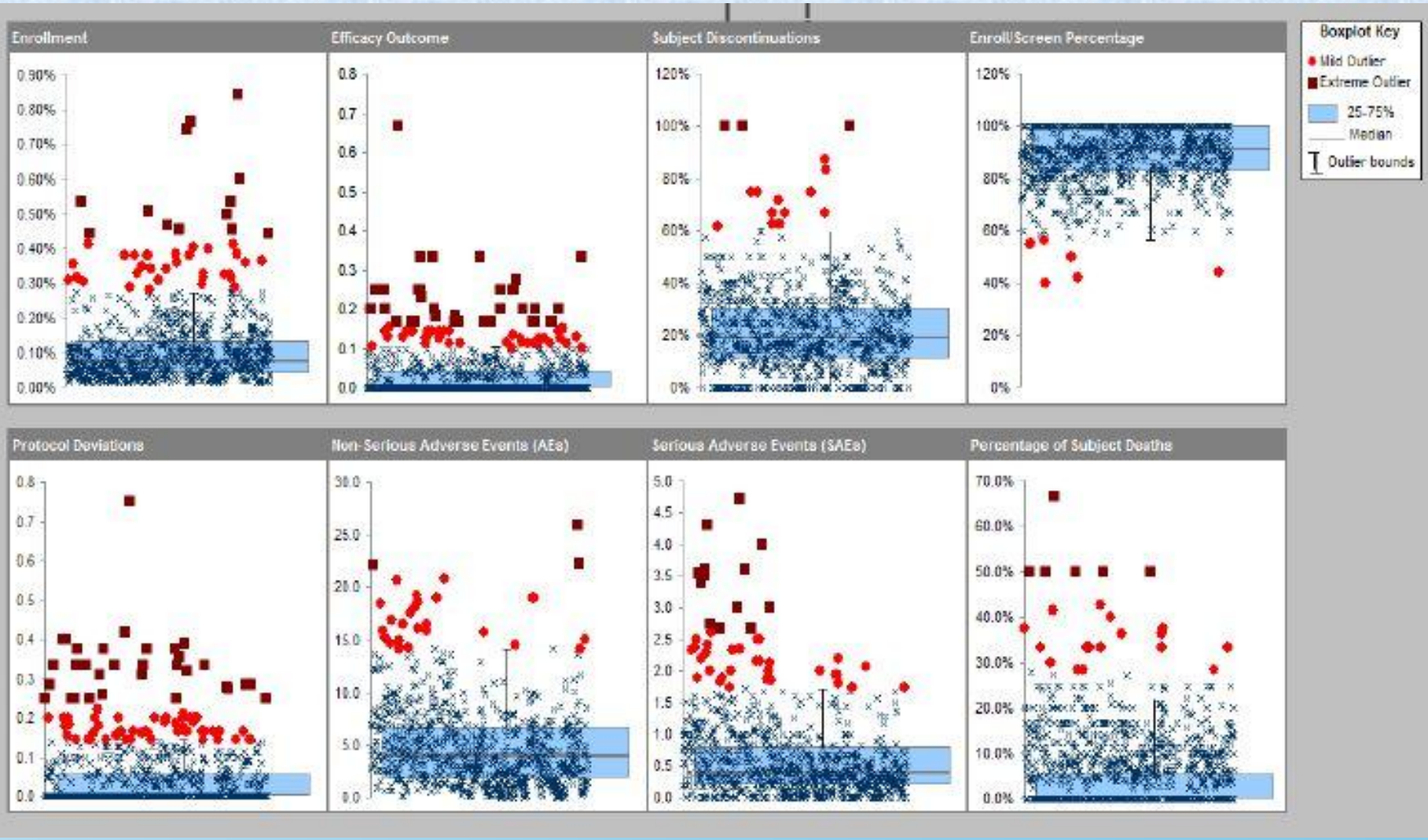
PDUFA-Related: Selection of Site

- Site selection is a joint process: Review Divisions & OSI
- Site selection considerations:
  - A specific safety concern at a particular site or sites
    - Based on review of AEs, SAEs, deaths, or discontinuations
  - A specific efficacy concern based on review of site specific efficacy data
    - Final outcome driven by a particular site or sites
    - Efficacy outcome different than expected based on mechanism of action of drug
  - Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results
  - History of clinical investigator

Criteria for PDUFA International Inspections

- Insufficient domestic data
- Only foreign data are submitted to support an application;
- Domestic and foreign data show conflicting results pertinent to decision-making; or
- Serious issues that need resolution, e.g., suspicion of fraud, scientific misconduct, human subject protection violations.

CDER Risk-based Site Selection Tool Pilot



Goals of Inspections: PDUFA

Assessment of the following:

- Clinical Investigator Qualifications
  - Training/Experience/CV review
- Clinical investigator oversight of study
  - In-depth knowledge of protocol/study plan
  - Selection of competent staff for delegation of responsibilities
- Clinical study center/site
- Informed consent procedures
- IRB approval
- Adherence to study protocol
- Test article accountability
- Recordkeeping

Focus of Inspection

The FDA Inspection (Audit) compares

- Source Document Medical Record Data

  vs

- Case Report Forms

  vs

- Data Listing Submitted to NDA
  - Primary efficacy measurements
  - Adverse events
  - Safety data: Labs, ECG, etc.

Verify

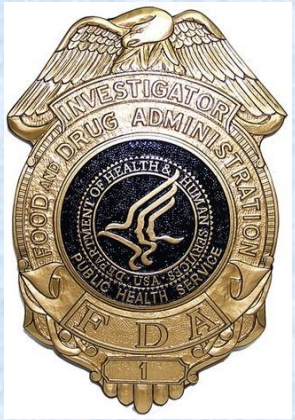
- Source of subjects; Did subjects exist?
- Did they have the disease under study?
- Did they meet inclusion/exclusion criteria?
- IRB Review Obtained? Consent obtained?
- Adherence to protocol?
- Drug Accountability? Blinding of data?

Inspections…

- **Are FACT finding**
- **Require EVIDENCE**
- **Require ORGANIZATION and TIME MANAGEMENT**
- **Are REGULATORY**
  - What is said could end up in court

To Lawfully Inspect (per 501(a)(1)(B)), FDA Must…

- **Show credentials**
  - Required by law to be shown upon starting an inspection
  - Displayed to the top management official (“owner, operator, agent in charge”)
  - Management may examine credentials and record the number and name
  - Credentials are <u>not</u> to be photocopied



- **Issue Notice of Inspection**

Notice of Inspection

- Also known as the FDA-482
- Must be issued to start the inspection (except for international sites)
- All team members must sign
- Original given to firm and copy included in the Establishment Inspection Report

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1. DISTRICT OFFICE ADDRESS & PHONE NO.

TO	2. NAME AND TITLE OF INDIVIDUAL	3. DATE
	4. FIRM NAME	5. HOUR a.m.
	6. NUMBER AND STREET	5. HOUR p.m.
	7. CITY AND STATE & ZIP CODE	8. PHONE NO. & AREA CODE

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8530 or by email at ombuds@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME(S) AND TITLE(S) *(FDA Employee(s))*

The FDA inspection ends…

- **Formal Close Out**
- **May include:**
  - Sample Collections
  - Affidavits (domestic)
  - Issuance of FDA 483, Inspectional Observations

After an Inspection Is Completed

- ORA may issue a Form FDA-483 at close of inspection
  - The observations listed on a Form FDA 483 lists inspectional observations
  - Immediately available via FOI
- ORA Prepares the Establishment Inspection Report (EIR)
  - Prepared by field investigator
  - Includes exhibits supporting all observations including deficiencies
  - Recommends inspection classification
  - Submitted to OSI for review
- OSI Prepares Review of EIR and pertinent exhibits
  - Makes final classification of the inspection
  - Informs the Review Division (NDA review) via internal report (Clinical Inspection Summary). Includes recommendation on data reliability.
- OSI Prepares written communication to inspected party:

  THE LETTER

Form FDA 483

- Observations listed in order of significance
- Must be objective and supported by evidence
- Guidance documents cannot be referenced on FDA 483
- Everyone present at issuance signs the first and last page of the FDA 483 and initials each intervening page in the signature block

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Regarding your conduct of protocol

OBSERVATION 1

Compliance Classifications

NAI - No Action Indicated

Inspected Entity is in compliance

VAI - Voluntary Action Indicated

Minor deviation(s) from the regulations

Voluntary correction is requested

OAI - Official Action Indicated

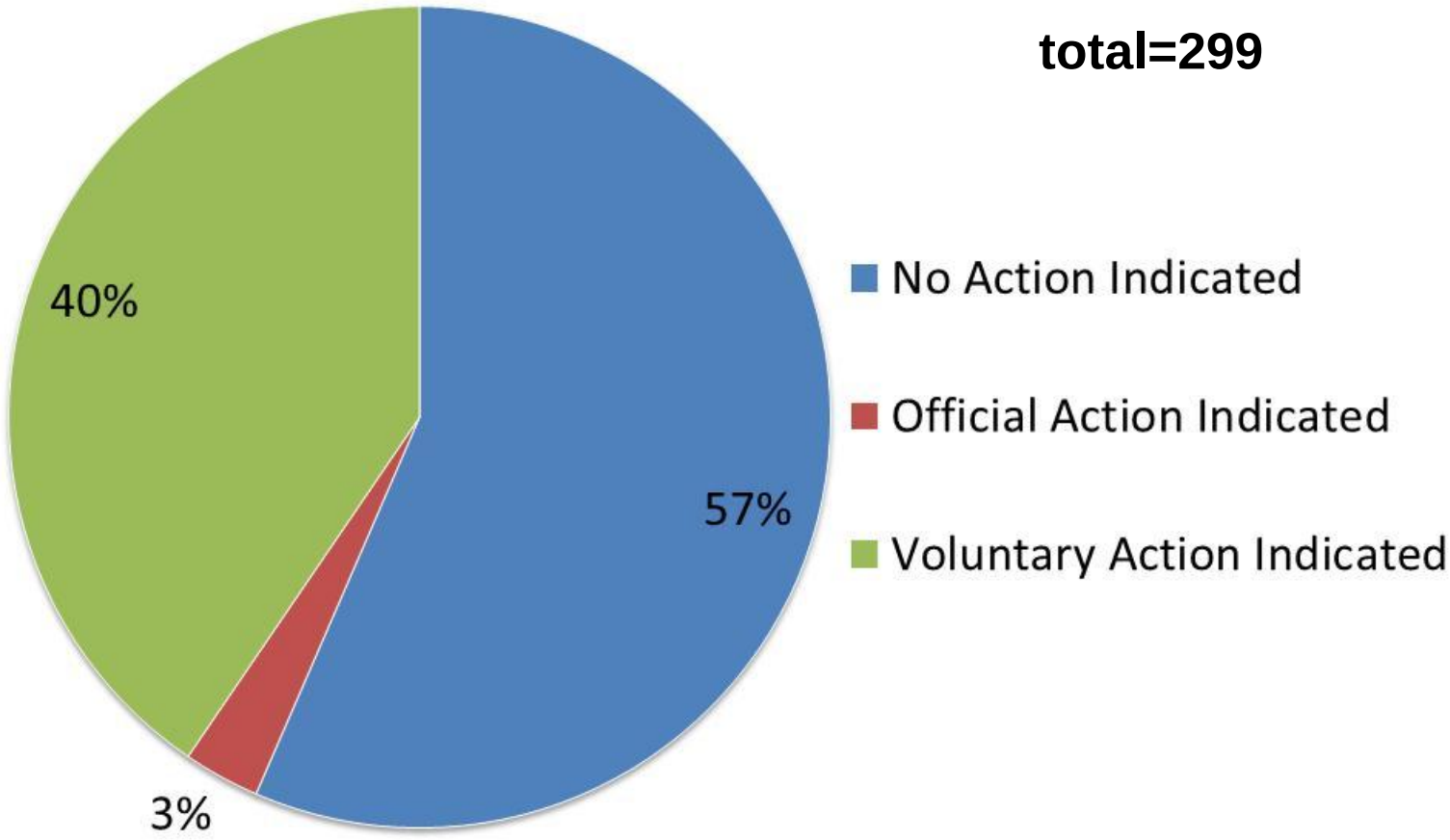
Serious non-compliance requiring regulatory or administrative action by FDA

Recommendations for Response

- Focus on the regulatory requirement(s) associated with each observation
- Consider root-cause analysis – is it isolated or are there system-wide and global implications
- Be specific (e.g. observation-by-observation), complete and realistic
- Provide all previous corrective actions
- Provide time frames for future correction
- Provide method of verification and/or monitoring for corrections

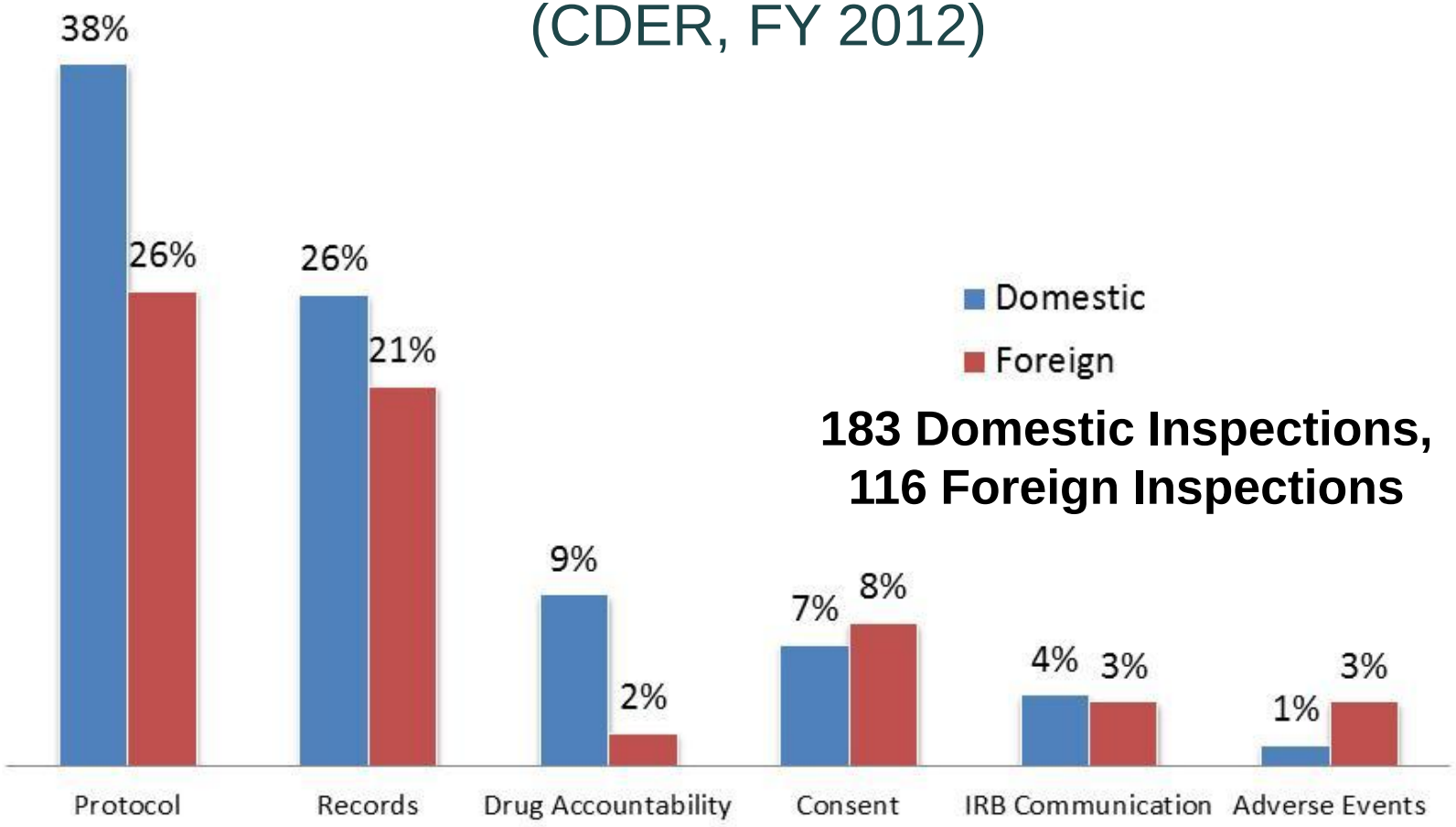
Clinical Investigator Inspections Final Classification*

(FY 2012)



*Based on Letter Issue date; Includes OAI Untitled Letters, [OSI database as of January 24, 2013]

Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued* (CDER, FY 2012)



*Based on letter issue date; Inspections may have multiple deficiencies, [OSI database as of January 24, 2013]
Note that this does not denote number of inspections completed in FY 2012, but rather number of inspection reports evaluated and closed in FY2012

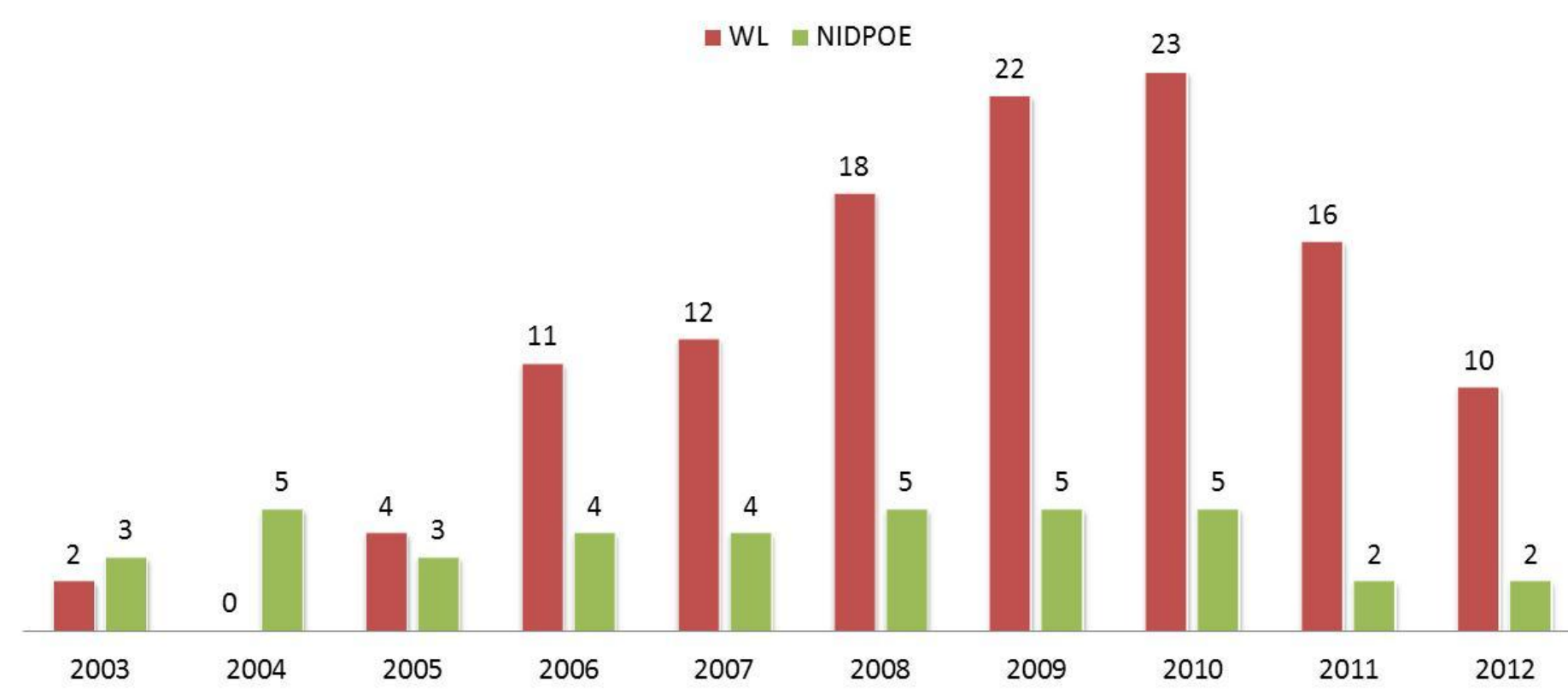
Consequences of Non-Compliance: OAI (not all inclusive)

- **Clinical Investigator**
  - Warning Letter
  - Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
  - Notice of Opportunity for Hearing (NOOH)
  - Consent Agreements
    - Restricted Agreement
    - Full Disqualification
  - Disqualification by Hearing or Commissioner
  - Debarment

Impact of Data Reliability Issues

- Additional Actions to Evaluate Data Reliability
  - Additional inspections
    - CIs, sponsors/monitors, CROs
  - Third party audits
  - New studies
- Impact on Approval
  - Depending on the scope, nature and risk
    - No effect on approval; approval may be granted
    - Approval may be delayed for further inspections and analyses
    - Post-marketing studies may be required
  - Non-approval (Complete Response)

BIMO Warning/NIDPOE Letters*
(CDER, FY 2003 - FY 2012)



- *Based on letter issue date [OSI database as of January 24, 2013]
- BIMO = Bioresearch Monitoring (Clinical Investigators, Sponsor/CRO/Sponsor-Investigator (GCP), IRB, BEQ, GLP)
- NIDPOE = Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

Clinical Investigator Regulatory Actions*
(CDER, FY 2003 - FY 2012)

Action	FY03	FY04	FY05	FY06	FY07	FY08	FY09	FY10	FY11	FY12*
WL**	1	0	0	6	10	12	18	13	13	5
NIDPOE	3	5	3	4	4	5	5	5	2	2
NOOH	1	1	0	1	1	1	2	1	2	1
CA-Restricted	1	1	1	3	1	2	0	3	0	0
CA-Full DQ	1	1	2	0	2	6	3	3	2	0
DQ-Hearing/Commissioner	1	0	0	0	0	4	0	2	1	1

WL = Warning Letter
NIDPOE = Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
NOOH = Notice of Opportunity for Hearing
CA = Consent Agreements (Restricted Agreements)
CA = Consent Agreements (Full Disqualification)
DQ = Disqualification by Hearing or Commissioner

*Based on letter issue date [OSI database as of January 24, 2013]
**WLs are informal and advisory in nature, not regulatory actions (FDA Regulatory Procedures Manual Chapter 4, Section 1-1)

Timeframe for Submission of Post-Inspection Responses

- **Intended to facilitate the timely issuance of Warning Letters (WLs) by establishing a timeframe for the submission of post-inspection responses to an FDA-483**
- **Industry has no more than 15 working days to respond to a 483 before FDA moves ahead with the issuance of a WL (if FDA determines that a WL is appropriate)**
- **Meant to eliminate delays in Agency's ability to take prompt enforcement action**

Case Study #1

- **OSI received a report from Sponsor:**
  - Significant GCP non-compliance was found during the sponsor's audit of site.
  - Site closure
    - Problems with informed consent
    - Major protocol violations
    - Forged signatures

Inspection

- Inclusion criteria not documented
- Source documents were not available to support the data recorded in the case report forms for all 12 subjects enrolled.
- Baseline Pulmonary Function Tests not performed at required timeframes
- Baseline Chest X-rays not performed
- Screening laboratory tests not performed
- Telephone contacts were not conducted by the investigator
- Inadequate records
- Legally effective informed consent was not obtained from 4 subjects

Inspection

- **Follow-up subject interviews were conducted to confirm forged subjects' signatures**
  - 4 subject's signatures were in question
  - 2 subject's could not be located
  - 2 subject's agreed that signature was not theirs; however, only one subject was willing to sign an affidavit

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)

- **Investigator was offered an opportunity to respond in writing,**

  or

- **Respond and offer new evidence at an informal conference,**

  or

- **Offered the option of entering into a consent agreement and terminate the administrative proceeding.**

Disqualification

- **OSI issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)**
  - Failure to personally conduct or adequately supervise the study
    - Investigator failed to adequately supervise the study coordinator
    - Study coordinator forged PI's signature on data query forms
    - PI felt the role of the monitor is to ensure that the study is conducted with the guidelines set by the sponsor
  - Failure to obtain informed consent
  - Failure to conduct the study according to the protocol

Cont.

- **Failure to maintain adequate and accurate records**
  - The case report forms (CRFs) for baseline visits for at least six subjects document that the Hemoccult (guaiac) test required by the protocol was performed; however, study records contain notes indicating that the subjects denied or could not recall that this test was performed
  - Source documents were not available to support CRF entries for all 12 subjects enrolled (lost due to hurricane)

Do's and Don't For Investigators: DO

- Follow the current protocol
- Personally conduct or supervise investigation(s)
- Ensure that all persons assisting in conduct of studies are informed of their obligations
- Ensure informed consent (21 CFR 50) and IRB review, approval , and reporting (21 CFR 56) requirements are met
- Obtain the informed consent of each human subject to whom the drug is administered

Do's and Don't For Investigators:DO

- **Notify the sponsor before making changes in the protocol.**
- **Notify the IRB and obtain IRB approval before making changes in the protocol.**
- **Report adverse events to the sponsor.**
- **Maintain adequate and accurate records.**
- **Make records available for inspection.**
- **Comply with all other requirements in 21 CFR 312**
- **Report Financial Interests to the Sponsor (21 CFR 312)**

*(Form FDA 1572: #9. Commitments)

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8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

('WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

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Do's and Don't For Investigators: DON'T

- Over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- Erase, white-out or obliterate original data entry either in CRFs or medical charts
- Accept suggested changes to study data without checking the source documents or without justification for such changes
- Backdate the consent forms and signatures
- Forget to obtain IRB approval of consent form revisions
- Revise the protocol without obtaining the sponsor's written concurrence

Improve Process — Be Proactive

- **Address human factors in systems**
  - Hire experienced, qualified staff
  - Avoid conflicts of interest/financial incentives
  - Decrease number of times data are handled

- **Create systems that limit opportunity for errors**
  - Simplify protocol and outcomes assessed
  - Be realistic about the amount of data to be collected
  - Standardize systems and formats where possible
  - Use validated instruments/definitions
  - Write down all procedures (SOPs). Use checklists.
  - Don’t re-invent the wheel
  - Keep amendments to a minimum and check the CRFs and consent form against each change

Improve Process — Be Proactive

- **Develop an integrated framework**
  - Data and Safety Monitoring Plan, Data Management Plan, Quality Assurance Plan, Data Analysis Plan
- **Insist on training and then test it**
- **Think very carefully about unblinding procedures**
- **Have a disaster plan**
- **Do beta-testing/dry-runs**
- **Have weekly team meetings/calls**
- **Do real-time cleaning of the data**
- **Audit yourself — be open and honest**

Compliance & Enforcement

- Links to information about clinical investigators who have and/or are participating in clinical trials of pharmaceutical products as well as regulatory correspondence and restrictions resulting from noncompliance observed during bioresearch monitoring (BIMO) inspections.
  - Clinical Investigator Inspection List, Bioresearch Monitoring Information Systems (BMIS) files, Warning Letters, NIDPOE Letters, Lists of Disqualified or Restricted or Debarred Investigators, Code of Federal Regulations, etc.

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm

CENTER FOR DRUG EVALUATION AND RESEARCH

Compliance Information

http://www.fda.gov/ICECI/default.htm

Guidances of Interest

- **FDA Inspections of Clinical Investigators-Information sheet**

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf

- **Guidance for Industry-Investigator Responsibilities**

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Guidances of Interest

- **Statement of Investigator (Form FDA 1572) Frequently Asked Questions**

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

- **Guidance for Industry - Acceptance of Foreign Clinical Studies**

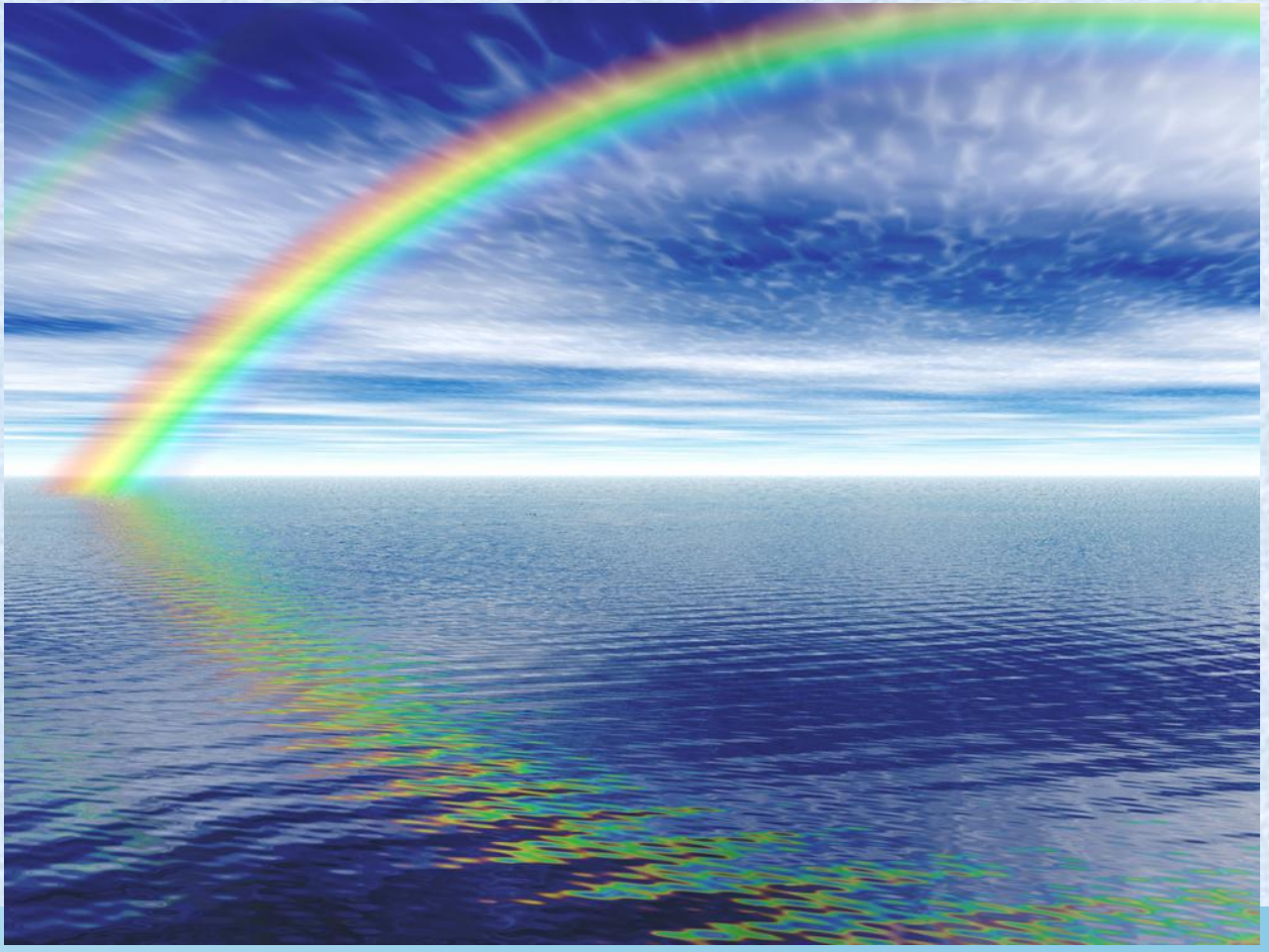
  http://www.fda.gov/RegulatoryInformation/Guidances/ucm124932.htm

Guidances of Interest

- **Guidance for Industry and FDA Staff- Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions March 2012**

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

Thank you



QUESTIONS??

Contact Information

- **The Office of Scientific Investigations can be contacted for questions, comments, or complaints about Investigational New Drug Research.**

E-mail: dsi@fda.hhs.gov
Telephone: (301) 796-3150
Fax: (301) 847-8748

Complaints: **CDER-OSI-GCPReferrals@fda.hhs.gov**

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